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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/374,967	08/16/99	DHUGGA K	5718-55

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EXAMINER	
SCHMIDT,M	
ART UNIT	**PAPER NUMBER**
1635	9

DATE MAILED: 07/05/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/374,967	DHUGGA ET AL.	
	Examiner	Art Unit	
	Mary Schmidt	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-15, 23, 24, 32, 33, 41-45, 49-59, 65-71 & 73-75 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-15, 23, 24, 32, 33, 41-45, 49-59, 65-71 & 73-75 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

KATRINA TURNER
PATENT ANALYST

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-13, 15, 24, 33, 41-44, 50-52, 71 and 73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-13, 15, 24, 33, 41-44, 50-52 and 71 are indefinite for the language "hybridizes... under stringent conditions" since neither the art nor the specification as filed provide the conditions which define stringent conditions. As such, the metes and bounds of the scope of possible nucleic acid sequences are not clear which would hybridize to the claimed sequences.

Claim 15 is indefinite since the ending is missing. It appears there should be a step (g) which was inadvertently omitted.

Claims 41, 43 and 73 lack antecedent basis since they depend on canceled claims.

In claims 56, 65 and 66, "said nucleotide sequence" lacks antecedent basis.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-15, 23-24, 32-33, 41-45, 49-59, 65-71 and 73-75 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to nucleic acid and protein sequences encoding any plant GDP-mannose pyrophosphorylase, expression cassettes for expressing any plant GDP-mannose pyrophosphorylase, plant cells and transgenic plants stably transformed with the gene expressing any plant GDP-mannose pyrophosphorylase, and methods using said constructs.

The specification as filed teaches the sequence of the maize GDP-mannose pyrophosphorylase gene in SEQ ID NO:1 and the sequence of the maize GDP-mannose pyrophosphorylase protein in SEQ ID NO:2. The specification teaches prophetically transformation of plant cells and construction of transgenic plants expressing said sequences. Neither the art not the specification as filed teach the sequences of other plant GDP-mannose pyrophosphorylase sequences at the time the invention was made (although the art is replete with microbial and yeast GDP-mannose pyrophosphorylase sequences).

The claims as drawn not only encompass any possible plant GDP-mannose pyrophosphorylase gene or protein sequence, but any sequence which hybridizes to the disclosed

SEQ ID NO:1, any sequence having 90% identity to the disclosed SEQ ID NO:1, at least 20 nucleotides of SEQ ID NO:1, or any sequence which hybridizes to the at least 20 nucleotides of SEQ ID NO:1, any antisense to any plant GDP-mannose pyrophosphorylase gene, any variants (substitutions, deletions, or additions) of the protein of SEQ ID NO:2, or any recombinant plant having any sequence encoding an enzyme in a galactomannan biosythetic pathway. Thus the claims are drawn to a broad scope of possible nucleic acid and protein sequences. Further the breadth extends to any plant cell or plant expressing said sequences.

First, it would not have been clear to one of skill in the art at the time the invention was made what the metes and bounds of the genus of possible sequences encompassed by the invention as broadly claimed would have been. Upon search of the prior art, sequences of GDP-mannose pyrophosphorylase were primarily found from microbes and yeast, but not from plant. Keller et al. teach in the post-art (The Plant journal: for cell and molecular biology. July 1999, vol. 19 (2), p. 131-141) that "GDP-mannose pyrophosphorylase (GMPase, EC 2.7.7.22) catalyzes the synthesis of GDP-D-mannose and represents the first committed step in the formation of all guanosine-containing sugar nucleotides found in plants which are precursors for cell wall biosynthesis and, probably more important, the synthesis of ascorbate." (See abstract) However, an assumed related functionality between major components of biosynthetic pathways common to all plants would still not lead one of skill in the art at the time the invention was made to identify a clear set of structural parameters for which all such GDP-mannose pyrophosphorylase genes would have so that there would have been expectation to know based on structure whether a

sequence will function as a plant GDP-mannose pyrophosphorylase. For the claims which broadly read on any sequence which hybridizes to at least a 20 base portion of SEQ ID NO:1, and any variant of the protein of SEQ ID NO:2, the genus would have an expectation in the art to read on multiple sequences which have no related function to a plant GDP-mannose phosphorylase.

In view of the breadth of genus of possible sequences, one skilled in the art would not have been in possession of the scope of possible sequences claimed, and thus not in possession of the scope of expression constructs, plant cells and transgenic plants expressing the claimed putative sequences. Neither the art nor the specification as filed teach a representative number of species for the breadth of the genus of possible sequences claimed.

One of skill in the art was in possession of the sequences of SEQ ID NO:1 and SEQ ID NO:2, the nucleic acid and protein sequences of maize GDP-mannose phosphorylase.

5. Claims 1-15, 23-24, 32-33, 41-45, 49-55, 65-71 and 73-75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NOS:1 and 2, expression cassettes comprising said sequences, plant cells and transgenic plants comprising said sequences, methods of expressing said sequences or antisense to said sequences in a plant cell or plant, does not reasonably provide enablement for the scope of possible nucleic acid sequences or protein sequences claimed nor use thereof in plant cells or plants. The specification does not enable any person skilled in the art to which it pertains, or with which it is

most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims not described above are claims 14-15, 45, 49-55 and 74-75. Claims 14-15 are drawn to methods for over-expressing GDP-mannose in any plant. Claims 49-59 are drawn to methods for down-regulating the expression of GDP-mannose pyrophosphorylase via transforming a plant cell with at least one nucleotide sequence encoding an antisense RNA to any GDP-mannose pyrophosphorylase. Claims 74-75 are drawn to methods for down-regulating levels of GDP-mannose by cosuppression, comprising transforming a plant cell GDP-mannose pyrophosphorylase with at least one nucleotide sequence encoding a truncated enzyme of a GDP-mannose biosynthetic pathway.

The specification as filed teaches the sequence of the maize GDP-mannose pyrophosphorylase gene in SEQ ID NO:1 and the sequence of the maize GDP-mannose pyrophosphorylase protein in SEQ ID NO:2. The specification teaches prophetically transformation of plant cells and construction of transgenic plants expressing said sequences. Neither the art not the specification as filed teach the sequences of other plant GDP-mannose pyrophosphorylase sequences at the time the invention was made (although the art is replete with microbial and yeast GDP-mannose pyrophosphorylase sequences).

As argued above, the scope of possible sequences claimed was not in possession of one skilled in the art at the time the invention was made. Further, one skilled in the art would have to

practice undue experimentation to make and use the scope of possible sequences claimed, thus including use of said sequences in plants.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or

binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427). Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

The assertion that the disclosed sequences have biological activities similar to any other possible isolated sequence having homology, or which hybridizes to the disclosed sequences cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even

examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). In the transforming growth factor (TGF) family, Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF-β1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). Similarly, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al.

(2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to use the claimed scope of nucleic acids and polynucleotides to make biologically active plant GDP-mannose pyrophosphorylase without resorting to undue experimentation to determine what the specific biological activities of the possible claimed sequences are.

Due to the large quantity of experimentation necessary to determine an activity or property of any sequence such that it can be determined how to use the claimed nucleic acids or polynucleotides encoding any plant GDP-pyrophosphorylase, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity, and the breadth of the claims which fail to recite particular biological activities and also embrace a broad class of structural fragments and variants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

6. Claims 56-59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 56-59 are drawn to methods for manipulating gum production in a plant of interest via transforming plant cells with at least one nucleic acid sequence encoding an enzyme in a galactomannan biosynthetic pathway or an antisense RNA thereto.

The specification as filed does not teach by way of example that the disclosed maize GMP-mannose pyrophosphorylase nor any other such possible species of pyrophosphorylase or any possible protein in any plant galactomannan biosythetic pathway will manipulate gum production in any plant of interest.

Neither the specification nor the art provide one of skill in the art with the necessarily nexus to teach how to manipulate gum production in any plant as broadly claimed by either increasing or decreasing the expression of any plant galactomannan biosythetic pathway protein.

Stephanopoulos et al. (TIBTECH Vol. 11, pages 392-396, 1993) and DeLuca (AgBiotech News and Information Vol. 5, No. 6, pages 225N-229N, 1993) are relied upon to teach the unpredictability in the art for predicting phenotypic function based on manipulation of one gene/protein in a biosynthetic pathway in plants.

Further, the art teaches that gum production varries in different species of plants as to the composition of the gum such that the ratio of different components of the gum differs significantly.

In view of the unpredictability in the art as to how increasing or decreasing any particular component of a biosynthetic pathway would effect a particular phenotypic change, one skilled in the art would have to practice "trial and error" experimentation to practice the invention as broadly claimed. Neither the art nor the specification as filed provide guidance as to how increasing or decreasing production of any galactomannan biosynthetic pathway component or any GDP-mannose pyrophosphorylase in any recombinant plant would be useful for manipulation of gum production.

7. SEQ ID Nos 1 and 2 were found to be free of the prior art. No sequences having 90% homology nor 20 base pairs of SEQ ID NO:1 were found in the search of SEQ ID NO:1.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst whose telephone number is (703) 305-3413.

M. M. Schmidt
June 28, 2001

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER